

Disruption and therapeutic rescue of autophagy in a human neuronal model of Niemann Pick type C1.

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Public Summary:

Niemann Pick type C1 (NPC1) is a devastating childhood neurologic disease that shares many similarities with Alzheimer's disease. This has prompted many researchers to call NPC1 "childhood Alzheimer's". Children affected with NPC1 often show symptoms of the disease very early in life, losing basic developmental milestones such as walking and talking. NPC1 has no cure or treatment, and affected children progress to develop severe dementia and death. NPC1 is caused by a genetic defect that results in abnormal distribution of cholesterol inside the cell. Cholesterol is an essential component of cell membranes, and is indispensable for cells to function properly. However, it is unclear how abnormal cholesterol distribution causes neuronal failure in NPC1, and why neurons are much more sensitive to this defect compared to other affected cell types. Until recently, we had been unable to study live human NPC1 neurons to start to answer these questions. For this reason, we used human embryonic stem cells (hESC) to generate neurons that mimic the features of NPC1 disease. We examined human NPC1 neurons and found that they have abnormal mitochondria that are shortened or "fragmented". Mitochondria have an essential role in the production of energy for the cell. For this reason they are constantly being "remodeled" and "recycled" by a process called "autophagy". We found that autophagy is abnormal in human NPC1 neurons, and that this interferes with normal turnover of mitochondria. Interestingly, these defects were much more severe in neurons compared to other cell types, which may explain why neurons are more sensitive to the effects of NPC1. We were able to rescue these defects in human NPC1 neurons by using drugs that modulate cholesterol distribution and autophagy. Mitochondrial and autophagy defects can injury synapses, which interferes with normal brain function and can ultimately cause neuronal death. Our approach establishes a platform to screen for compounds that can revert accumulation of cholesterol, mitochondrial fragments, and other autophagic intermediates in NPC1. Therefore, our study is starting to define a new route to effective drug development for NPC1 disease and related neurologic disorders like Alzheimer's disease.

Scientific Abstract:

An unresolved issue about many neurodegenerative diseases is why neurons are particularly sensitive to defects in ubiquitous cellular processes. One example is Niemann Pick type C1, caused by defects in cholesterol trafficking in all cells, but where neurons are preferentially damaged. Understanding this selective failure is limited by the difficulty of obtaining live human neurons from affected patients. To solve this problem we generated neurons with decreased function of NPC1 from human embryonic stem cells and used them to test the hypothesis that defective cholesterol handling leads to enhanced pathological phenotypes in neurons. We found that human NPC1 neurons have strong spontaneous activation of autophagy, and, contrary to previous reports in patient fibroblasts, a block of autophagic progression leading to defective mitochondrial clearance. Mitochondrial fragmentation is an exceptionally severe phenotype in NPC1 neurons compared to fibroblasts, causing abnormal accumulation of mitochondrial proteins. Contrary to expectation, these abnormal phenotypes were rescued by treatment with the autophagy inhibitor 3-methyladenine, and by treatment with the potential therapeutic cyclodextrin, which mobilizes cholesterol from the lysosomal compartment. Our findings suggest that neurons are especially sensitive to lysosomal cholesterol accumulation because of autophagy disruption and accumulation of fragmented mitochondria, thus defining a new route to effective drug development for NPC1 disease.